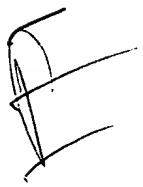

SB
SmithKline Beecham

CONFIRMATION

Tel: 44-181-975-6347
Fax: 44-181-975-6177

23 December 1999

Our Ref: MM/CBT/P32151EP

Mr S Haertinger
European Patent Office
D-80298 Munich
GERMANY

Dear Mr Haertinger

European patent Application No. 99303151.7-2215 in the name of SmithKline Beecham plc

This letter relates to the Communication from the EPO dated 25.10.99 regarding the aforementioned application and pursuant to Art.96(2) and Rule 51(2) EPC. Please find enclosed (in triplicate) a new set of claims in complete replacement for the claims currently on file at the EPO. There is also enclosed a table, entitled "P32151-Support for new claims" outlining the basis for the new set of claims in the application as filed originally. Accordingly Art.123(2) EPC is not contravened.

In addition, please find a completed Form 1002, designating two additional inventors whose names were omitted, in error, on the original designation form. Thus a request is respectfully made by the applicant for these additional inventors to be designated on the application.

Having regard to the Communication from the EPO, the applicant hereby respectfully requests that a new set of claims be considered by the Examining Division. It is believed that the present claim set overcomes the unity objection (Art.82 EPC) raised by the Examiner in the Communication. The applicant retains the right to file a divisional application to the non-elected subject-matter of the present application.

The applicant wishes to draw to the attention of the Examining Division a pending PCT application (WO 98/56787) in the name of Synthon B.V. and designating a European patent. This PCT application, having a filing date of 10th June 1997 with no claimed priority date, and a publication date of 17th December 1998 will be citable as prior art under Art.54(3) EPC against the subject matter of the present application entitled to the 6th October 1998 priority dates, provided the PCT application is progressed into the regional phase. On the assumption that the Synthon application will be progressed in Europe, the

amended claims are both novel over Synthon and are also entitled to at least the October priority date.

Claims 1 to 20 correspond to old claims 1,3 and 4 and relate to a particular crystalline form of paroxetine methane sulphonate, characterized by distinguishing IR and XRD peaks. This form of paroxetine methanesulfonate is not disclosed in the Synthon application. Whilst Example 1 of Synthon at page 10 describes the preparation of a methane sulphonate salt, it is evident from the characterising data disclosed in Table 1 on page 14 that it is not the same as that presently claimed. In particular the paroxetine mesylate described by Synthon has *inter alia* the following characteristic IR peaks: 1208, 1169, 1038, 962, 931 838 and 546 cm^{-1}. In contrast claim 1 of the present application covers paroxetine mesylate in crystalline form having *inter alia* the following characterstic IR peaks: 1603, 1513, 1194, 1045, 946, 830, 776, 601, 554 and 539 ± 4cm^{-1}. Infra red spectroscopy is a well-known technique for distinguishing between different forms of chemical products. Therefore paroxetine mesylate described in the Synthon application is a different polymorph and does not destroy the novelty of SB's claim 1 describing another polymorph of paroxetine mesylate.

Claims 2 to 19 are dependent upon claim 1 and accordingly are also novel.

Claim 20 (and its dependent claims 21 to 29) all relate to a pharmaceutical composition comprising from 1 to 200mg of paroxetine methanesulfonate, calculated on a free base basis. There is however no disclosure in the Synthon application of such a weight range, and accordingly claim 20 and its dependent claims must be novel. Whilst the Synthon application does refer on page 2 to prior published documents disclosing pharmaceutical compositions containing paroxetine hydrochloride hemihydrate (e.g. EP 223 403) there is no suggestion that pharmaceutical compositions comprising paroxetine methanesulfonate should be formulated in a similar manner to the hydrochloride salt. Indeed, the statement made by Synthon on page 9 lines 15-20 that "The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the *in vitro* release as well as good bioavailability after per oral application *in vivo*", implies that the methanesulfonate salt would not be formulated in identical manner with the known hydrochloride salt. Therefore it is irrelevant that the prior published document EP 223 403 discloses pharmaceutical compositions comprising from 1 to 200mg of paroxetine hydrochloride hemihydrate.

Claim 30 (and dependent claims 31 to 35) relate to processes for preparing paroxetine methanesulfonate using solvents not disclosed in the Synthon application. Whilst Example 1 of Synthon does disclose the use of ethyl acetate, this solvent is excluded by the proviso in claim 31.

Claim 36 relates to uses of paroxetine methanesulfonate not disclosed in the Synthon application and therefore must also be novel. (See page 6 lines 33 to 36 of Synthon).

Claims 27 to 44 are independent claims corresponding to claims 21 and 22 and are similarly novel.

As mentioned previously, Synthon is not citable with respect to inventive step of the amended claim set. Having regard to the question of obviousness of the mesylate form of paroxetine *per se*, the following observations are apposite.

Whilst it is true that the current commercial form of paroxetine is the hydrochloride it does not follow that all alternative acid addition salts of paroxetine will be suitable for use in a commercial product. For example, the present applicants have investigated various acid addition salts of paroxetine and have found that several salts, in particular, the acetate and maleate are not stable and cannot be used in a commercial product. In particular it was found that after four weeks storage at elevated temperature (80°C) both the acetate and the maleate had significant losses in their potency indicating that they would not be suitable for use in a commercial product requiring a satisfactory shelf life.

In developing a novel salt form of paroxetine, it cannot be predicted whether a crystalline product will be formed. Surprisingly the present applicants have found that paroxetine methanesulfonate does form a stable crystalline product which has several advantages in that it can be readily isolated which helps in its manufacture on a commercial scale and as it is stable it can also be formulated as a commercial product. Furthermore we have found paroxetine methanesulfonate to have high water solubility (at least 1.7g dissolves in 1g of water at 20°C) and very low hygroscopicity (using a standard hygroscopicity/stability test comprising exposure to 75% Relative Humidity at 40°C for 14 days, only 0.02% water was absorbed).

The advantageous properties of paroxetine methanesulfonate are confirmed by experiments carried out by Synthon. Thus WO98/56787 at page 16 provides data suggesting that paroxetine methanesulfonate has advantages in terms of high solubility, low hygroscopicity and good stability. A corresponding US patent (US-A-587 4447) has also been granted to Synthon. In obtaining patent grant Synthon submitted the attached declaration of Dr Peters demonstrating that paroxetine methanesulfonate has advantageous properties when compared with at least four alternative salts, namely the maleate, acetate, tartrate and fumarate.

In summary it is apparent that not all acid addition salts of paroxetine are suitable for use in a commercial product. Therefore the present applicants have indeed used inventive skill in identifying a particular salt of paroxetine, namely the methanesulfonate, which can be advantageously formulated as a commercial product.

The current application is being progressed under the accelerated prosecution provisions governed by PACE. Accordingly the applicant has provided a full and frank disclosure of the patentability of the invention as claimed herein. We trust that the information provided will enable the application to proceed to grant quickly and so we look forward to receiving the Rule 51(4) Communication from the EPO as soon as possible. However in the unlikely event that the Examining Division are minded to refuse the application, oral proceedings are hereby requested.

Yours sincerely

Clive B. Thompson
Authorized Representative

ERFINDERNENNUNG / DESIGNATION OF INVENTOR / DESIGNATION DE L'INVENTEUR

(falls Anmelder nicht oder nicht allein der Erfinder ist) / (where the applicant is not the inventor or is not the sole inventor) / (si le demandeur n'est pas l'inventeur ou l'unique inventeur)

Zeichen des Anmelders oder Vertreters Applicant's or representative's reference Référence du demandeur ou du mandataire (max. 15 Positionen / max. 15 spaces / 15 caractères au maximum) MM/CTP32151	Nr. der Anmeldung oder, falls noch nicht bekannt, Bezeichnung der Erfindung Application N° or, if not yet known, title of the invention N° de la demande ou, si ce dernier n'est pas encore connu, titre de l'invention NOVEL COMPOUND

In Sachen der obenbezeichneten europäischen Patentanmeldung nennt (nennen) der (die) Unterzeichnete(n) [1]
In respect of the above European patent application I (we), the undersigned [1]
En ce qui concerne la demande de brevet européen susmentionnée le (s) soussigné(s) [1]

EPO - Munich
40
04 Jan. 2000

SmithKline Beecham p.l.c.
New Horizons Court, Brentford, Middlesex, TW8 9EP, United Kingdom
als Erfinder [2]:
do hereby designate as inventor(s) [2]:
désigne(nt) en tant qu'inventeur(s) [2]:

Victor Witold JACEWICZ and Michael URQUHART of SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN, United Kingdom

☐ (Weitere Erfinder sind auf einem gesonderten Blatt angegeben) / (Additional inventors indicated on supplementary sheet) / (les autres inventeurs sont mentionnés sur une feuille supplémentaire).

Der (Die) Anmelder hat (haben) das Recht auf das europäische Patent erlangt [3]
The applicant(s) has (have) acquired the right to the European patent [3]
Le(s) demandeur(s) a (ont) acquis le droit au brevet européen [3]

☐ gemäß Vertrag vom _____
under an agreement dated _____
par contrat en date du _____

☒ als Arbeitgeber
as employer(s)
en qualité d'employeur(s)

☐ durch Erfolge
as successor(s) in title
par transfert successoral

Ort/Place/Lieu Brentford, Middlesex, England Datum/Date 23 December 1999

Unterschrift(en) des (der) Anmelder(s) oder Vertreter(s) /
Signature(s) of applicant(s) or representative(s) /
Signature(s) du (des) demandeur(s) ou du (des) mandataire(s)

Clive Thompson

THOMPSON, Clive Beresford
European Patent Attorney, Agent for the Applicant

Name des (der) Unterzeichneten bitte mit Schreibmaschine wiederholen. Bei juristischen Personen bitte die Stellung des (der) Unterzeichneten innerhalb der Gesellschaft mit Schreibmaschine angeben / Please type name under signature in case of legal persons, the position of the signatories in the company should also be typed / Le ou les noms des signataires doivent être également dactylographiés. S'il s'agit d'une personne morale, la position occupée au sein de celle-ci par le ou les signataires sera indiquée à la machine à écrire.

Fußnoten befinden sich auf der Rückseite / Footnotes overleaf / Les notes des renvois figure au verso
bitte wenden / P.T.O. / T.S.V.P.

EPA/EPO/OEB Form 1002 04.89

MM/CTP32151

Raum für Zeichen des Anmelders / Space for applicant's reference / Espace réservé à la référence du demandeur

Claims

1. Paroxetine methanesulfonate in crystalline form having *inter alia* the following characteristic IR peaks: 1603, 1513, 1194, 1045, 946, 830, 776, 601, 554, and 539 ± 4 cm^{-1}.; and/or the following characteristic XRD peaks: 8.3, 10.5, 15.6, 16.3, 17.7, 18.2, 19.8, 20.4, 21.5, 22.0, 22.4, 23.8, 24.4, 25.0, 25.3, 25.8, 26.6, 30.0, 30.2, and 31.6 ±0.2 degrees 2 theta.

2. A process for the preparation of a compound as claimed in claim 1 comprising crystallizing or re-crystallizing the compound from a solution of paroxetine methanesulfonate in a solvent.

3. A process according to claim 2 in which the solution of paroxetine methanesulfonate is prepared by treating paroxetine free base or an organic salt thereof with methanesulfonic acid or an ammonium or amine salt thereof.

4. A process according to claims 2 or 3 in which the solvent comprises toluene, an alcohol, an ester, a ketone, a halogenated hydrocarbon, a nitrile, or an ether, optionally in admixture with water, an ether, or a lower alcohol, or mixtures thereof.

5. A process according to any one of claims 2 to 4 in which the solvent forms an azeotrope with water and prior to isolation of the product water is removed by azeotropic distillation.

6. A process according to any one of claims 2 to 5 in which the crystallisation is promoted by inclusion of an anti-solvent to the solvent, in which the anti-solvent is an ether or hexane.

7. A process according to any one of claims 2 to 6 in which the crystallisation is conducted at elevated temperature followed by controlled cooling.

8. A process according to any one of claims 2 to 7 in which crystallisation is induced by the addition of a seed crystal.

9. A process according to any one of claims 2 to 8 in which crystallisation is conducted without the addition of a seed crystal.

10. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

11. A composition according to claim 10 in which the carrier comprises a disintegrant.

12. A composition according to claims 10 or 11 in which the carrier comprises a binder.

13. A composition according to any one of claims 10 to 12 in which the carrier comprises a colouring agent.

14. A composition according to any one of claims 10 to 13 in which the carrier comprises a flavouring agent.

15. A composition according to any one of claims 10 to 14 in which the carrier comprises a preservative.

16. A composition according to any one of claims 10 to 15 adapted for oral administration.

17. A composition according to claim 16 which is a tablet or capsule.

18. A composition according to any one of claims 10 to 17 wherein the compound is present in an amount ranging from 1 to 200mg, calculated on a free base basis.

19. Use of a compound according to claim 1 in the manufacture of a medicament for use in the treatment and/or prevention of any one or more of the Disorders.

20. A pharmaceutical composition comprising 1 to 200mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

21. A composition according to claim 20 comprising 10 to 50mg of paroxetine methanesulfonate, calculated on a free base basis.

22. A composition according to claim 20 or 21 comprising 10, 12.5, 15, 20, 25, 30 or 40mg of paroxetine methanesulfonate, calculated on a free base basis.

23. A composition according to any one of claims 20 to 22 wherein the carrier comprises a disintegrant.

24. A composition according to any one of claims 20 to 23 wherein the carrier comprises a binder.

25. A composition according to any one of claims 20 to 24 wherein the carrier comprises a colouring agent.

26. A composition according to any one of claims 20 to 25 wherein the carrier comprises a flavouring agent.

27. A composition according to any one of claims 20 to 26 wherein the carrier comprises a preservative.

28. A composition according to any one of claims 20 to 27 adapted for oral administration.

29. A composition according to claim 28 which is a tablet or capsule.

30. A process for the preparation of paroxetine methanesulfonate by precipitation (including crystallization or re-crystallization) from a solution of a paroxetine methanesulfonate, or spray drying or freeze drying a solution of a paroxetine methanesulfonate, wherein the solution of paroxetine methanesulfonate, comprises a solvent which is toluene, an alcohol, an ester, a ketone, a halogenated hydrocarbon, a nitrile, or an ether, optionally in admixture with water, an ether, or a lower alcohol, or mixtures thereof, with the proviso that the solvent for precipitation is not ethyl acetate.

31. A process according to claim 30 wherein the solvent forms an azeotrope with water and prior to isolation of the product water is removed by azeotropic distillation.

32. A process according to claim 30 or 31 in which the crystallization is promoted by inclusion of an anti-solvent to the solvent, in which the anti-solvent is an ether or hexane.

33. A process according to any one of claims 30 to 32 in which the crystallization is conducted at elevated temperature followed by controlled cooling.

34. A process according to any one of claims 30 to 33 in which the crystallization is induced by the addition of a seed crystal.

35. A process according to any one of claims 30 to 34 in which the crystallization is conducted without a seed crystal.

36. Use of paroxetine methanesulfonate in the preparation of a medicament for use in the treatment and/or prevention of any one or more of the disorders alcoholism, trichotillomania, substance abuse, anxiety, chronic pain, adolescent depression and dysthymia.

37. A pharmaceutical composition comprising 10 to 50mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

38. A pharmaceutical composition comprising 10mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

39. A pharmaceutical composition comprising 12.5mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

40. A pharmaceutical composition comprising 15mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

41. A pharmaceutical composition comprising 20mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

42. A pharmaceutical composition comprising 25mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

43. A pharmaceutical composition comprising 30mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

44. A pharmaceutical composition comprising 40mg of paroxetine methanesulfonate, calculated on a free base basis, and a pharmaceutically acceptable carrier.

P32151 Europe - Support for new claims

Claim	Support in application as filed (English text)
1	Combination of old claims 1, 3 & 4, & page 12 lines 6-9 & 12-15.
2	Old claim 6 & page 2 lines 1-3.
3	Combination of old claims 8 & 10, & page 2 lines 10-12, 22-23, & page 3 lines 6-7.
4	Old claim 13 & page 5 lines 12-16 & lines 26-28.
5	Old claim 14 & page 7 lines 4-9.
6	Combination of old claims 15 & 16, & page 8 lines 9-23 (especially lines 18 & 20) & page 7 line 20.
7	Old claim 17 & page 7 lines 23-24.
8	Old claim 18 & page 7 lines 25 & 32, & page 9 lines 26-31.
9	Old claim 19 & page 7 lines 25 & 32.
10	Old claim 20 & page 13 lines 21-23.
11	Old claim 21 & page 14 line 18.
12	Old claim 22 & page 14 line 21.
13	Old claim 23 & page 14 line 22.
14	Old claim 24 & page 14 line 32.
15	Old claim 25 & page 15 line 1.
16	Old claim 26 & page 13 line 30.
17	Old claim 27 & page 14 line 10.
18	Old claim 29 & page 14 line 2.
19	Old claim 30 & page 13 lines 26-27.
20	Combination of old claims 29, 20 & 1, & page 14 line 2.
21	Page 14 line 3.
22	Page 14 line 3.
23	Old claim 21 & page 14 line 18.
24	Old claim 22 & page 14 line 21.
25	Old claim 23 & page 14 line 22.
26	Old claim 24 & page 14 line 32.
27	Old claim 25 & page 15 line 1.
28	Old claim 26 & page 13 line 30.
29	Old claim 27 & page 14 line 10.
30	Page 1 lines 25-28, page 2 lines 1-2, & old claim 13 & page 5 lines 12-16 & lines 26-28. (NB claim contains a proviso to exclude disclosure in Example 1 of Synthon patent application).
31	Old claim 14 & page 7 lines 4-9.
32	Combination of old claims 15 & 16, & page 8 lines 9-23 (especially lines 18 & 20) & page 7 line 20.
33	Old claim 17 & page 7 lines 23-24.
34	Old claim 18 & page 7 lines 25 & 32, & page 9 lines 26-31.
35	Old claim 19 & page 7 lines 25 & 32.
36	Page 13 lines 4-15 & lines 26-27 excluding the uses disclosed in the Synthon application (at page 6 lines 33-36).
37	Page 14 line 3.
38	Page 14 line 3.
39	Page 14 line 3.
40	Page 14 line 3.
41	Page 14 line 3.
42	Page 14 line 3.
43	Page 14 line 3.
44	Page 14 line 3.

EPO - Munich
49
04 Jan. 2000

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
BENNEKER, et al.

Serial No: 08/872,023

Filed: June 10, 1997

For: 4-Phenylpiperidine Compounds

Group Art Unit: 1612

Examiner: Chang, C.

Atty. Dkt.: 06854.0002

RECEIVED
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DECLARATION UNDER 37 C.F.R. 1.132

I, Theodorus Hendricus A. Peters, do hereby declare as follows:

1. I am a co-inventor of the above-identified application.

2. I received a chemical laboratory engineering diploma (an "ing" diploma comparable to a bachelors degree) in 1984 from the technical school OLAN (Arnhem, The Netherlands). In 1989 I received a diploma (equivalent to a bachelors degree) in chemistry and in 1990 a general diploma (a "Drs." diploma comparable to a masters degree) in Chemistry, both from the University of Utrecht (Utrecht, The Netherlands). Subsequently in 1993 I completed my course work for a Ph.D.[1] in Chemistry, specialized in organic and organometallic chemistry, also at the University of Utrecht (Utrecht, The Netherlands).

3. I have been employed in the chemical research field since 1985 by several different employers including universities and private companies. In 1993 I joined Synthon BV, the assignee of the present application, as head of the Chemical Research and Development Department, and remain in this position to the present day.

4. I am familiar with the prosecution history of the present application, including the Office Action dated April 23, 1998. In order to further demonstrate the unobviousness of the present invention, I offer the following data on solubility and stability. Unless otherwise indicated, all data was determined/measured by me or by a subordinate under my direct supervision and control.

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[1] The defense of my thesis is expected to be done sometime next year after which the Ph.D. degree should be officially granted.

Solubility

The solubility of various paroxetine compounds was measured gravimetricly at 20°C by the following procedure. An exactly weighed amount (from about 50-200 mg) was stirred for at least one hour in a fixed amount of water (1 to 50 ml). When all the solid substance dissolved, an additional exactly weighed amount was added and stirred again for at least one hour. The addition and stirring was repeated whenever the substance fully dissolved. In the cases when a concentration of 1000 (or more) mg per ml was reached and there was still a clear solution (mesylate, besylate and tosylate) then the result is reported as "higher than 1000" mg/ml. When a suspension was observed after stirring, then the solid was filtered off, dried and weighed. The amount of compound soluble in the given volume of water was then calculated by the difference between the total added amount and the amount of the filtrate (maleate and acetate). In the cases of the fumarate and the tartrate, the solid was not able to be filtered off in a proper way. In these cases the solubilities are reported as "less than [the added amount]" per ml. The results are shown below:

Solubility of Paroxetine Compounds (mg per ml of water)	
paroxetine methane sulfonate (mesylate)	more than 1000
paroxetine benzene sulfonate (besylate)	more than 1000
paroxetine toluene sulfonate (tosylate)	more than 1000
paroxetine hydrochloride anhydrate	8.2
paroxetine hydrochloride hemihydrate	4.9
paroxetine maleate	7.0
paroxetine fumarate*	less than 7
paroxetine tartrate*	less than 7
paroxetine acetate	200

* published value
# novel comparison salt of paroxetine

The sulfonate salts of paroxetine which correspond to the present invention, exhibit over 5 times the solubility of the acetate salt and over 100 times the solubility of the other comparison

compounds. This dramatic increase in solubility exhibited by the sulfonate salts constitutes a significant and substantial improvement over the prior art paroxetine compounds (and over the novel, non-prior art, comparison compounds). The data shows that unlike other pharmaceutically acceptable salts which generally have a solubility of less than 10 mg/ml, the sulfonate salts have a solubility of greater than 1000 mg/ml. Such an increase in solubility by the use of a sulfonate salt was not predicted or suggested by any of the prior art teachings of which I am aware.

Stability

The solid state stability of various paroxetine compounds was measured using thermogravimetric analysis (TGA). TGA curves were produced using a Mettler Toledo TGA/SDTA851e in open aluminum oxide pans of 70 µl. The measurements were carried out with 15-20 mg samples under nitrogen with a flow rate of 70 ml per minute. The starting temperature was 25°C, heating at a rate of 10°C per minute and the measurements were stopped at 300°C. A blanc curve was recorded with an empty pan under the same conditions. This blanc curve was subtracted for each TGA. Between the measurements a calibration with the calibration weights in the module was performed. The TGA curves are set forth in Exhibits 1 and 2.

Exhibit 1 shows the thermal degradation of the following paroxetine compounds:

Inventive Compounds	Comparison Compounds
paroxetine methane sulfonate (mesylate)	paroxetine hydrochloride hemihydrate
paroxetine benzene sulfonate (besylate)	paroxetine free base
paroxetine toluene sulfonate (tosylate)	paroxetine maleate
paroxetine *p*-chlorobenzene sulfonate (*p*-chlorobesylate)	paroxetine fumarate#
	paroxetine tartrate#
	paroxetine acetate

novel comparison paroxetine salt

The Y-axis of the plot shown in Exhibit 1 indicates the amount of paroxetine compound while the X-axis indicates both the temperature and duration of the test. It should be noted that the curves have been separated for clarity. That is, the curves do not start at a common point on

the Y axis. The change in weight amount of each paroxetine compound relative to its own starting point can thus be clearly seen. The bar on the Y-axis provides a frame of reference by indicating the distance along the Y-axis that corresponds to a 10 mg change in the amount of the compound.

The stability of a pharmaceutical compound is a factor in determining its commercial or practical viability. The more rapidly (shorter time or lower temperature) that a compound degrades, the less stable the compound. Thus, the flatter the TGA curve (smaller ΔY), the lower the amount of degradation and the more stable the compound. Conversely, the greater the drop, the less stable the compound.

The TGA curves in Exhibit 1 show that the sulfonate salts of paroxetine have good to excellent stability and are more stable than any of the comparison compounds. In particular, the mesylate, besylate and tosylate salts are very stable, while the *p*-chlorobesylate salt is slightly more stable than the hydrochloride hemihydrate salt. Although both the hydrochloride hemihydrate and the *p*-chlorobesylate loose water at around 130 °C, the loosing of water for the hydrochloride is sharper than for the *p*-chlorobesylate. But, at higher temperatures the hydrochloride hemihydrate shows a bit more degradation than the *p*-chlorobesylate. Accordingly, the stability of these compounds is given as:

mesylate > besylate > tosylate >>> *p*-chlorobesylate > hydrochloride hemihydrate > fumarate > maleate > free base > tartrate >> acetate.

This result is surprising in that the sulfonate salts are more stable, and in some cases greatly more stable, than the commercially available form of paroxetine (the hydrochloride hemihydrate).

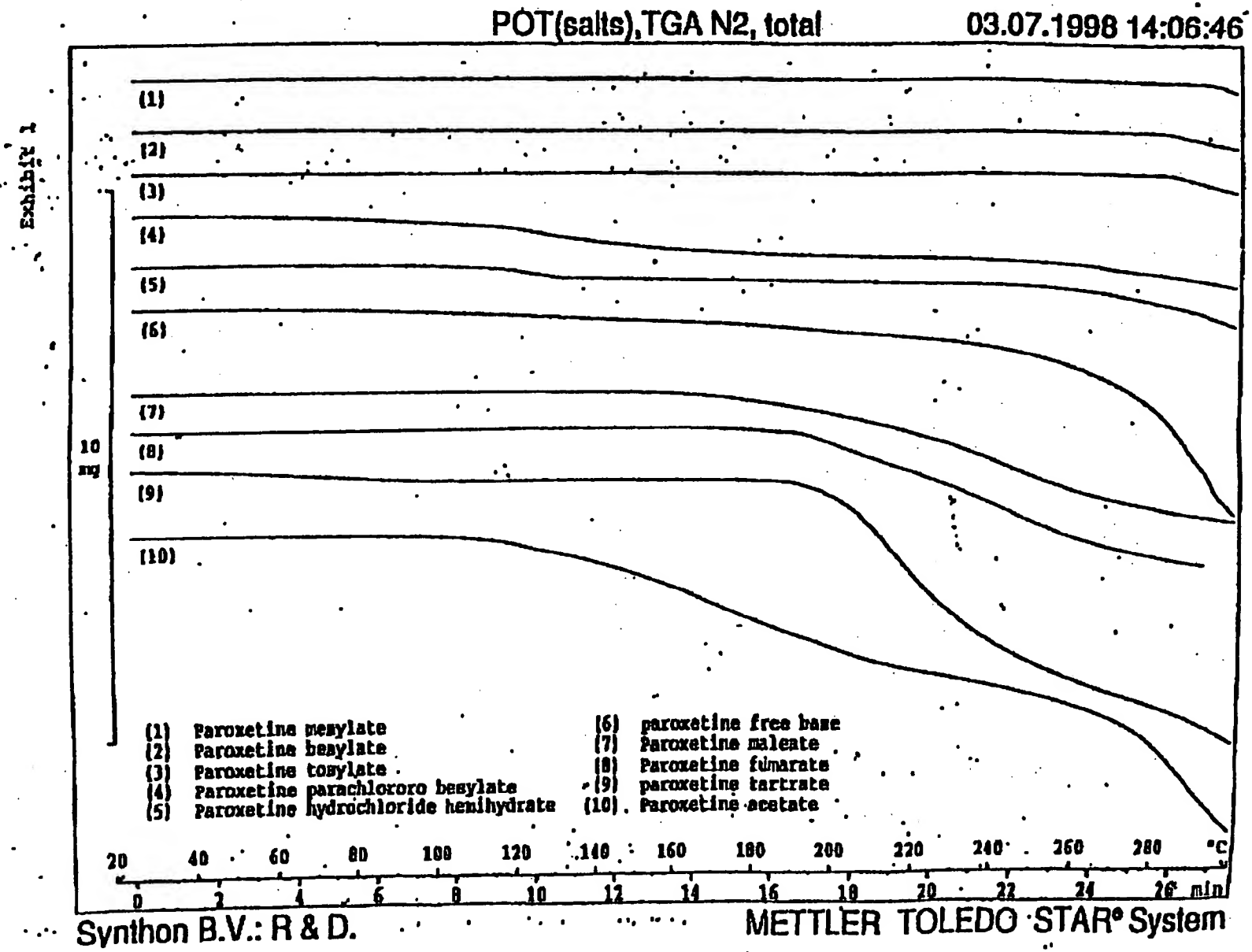
Exhibit 2 shows the magnified TGA curves for the mesylate, the free base (fresh and stored), the maleate, and the acetate forms, with each curve starting at the same point. It is apparent that degradation for the paroxetine free base (fresh and stored) and the acetate salt has begun by 60°C, and that by 120°C all of the comparison compounds including the maleate are clearly degrading and unstable. The mesylate compound, in contrast, does not begin to degrade until after 260°C.

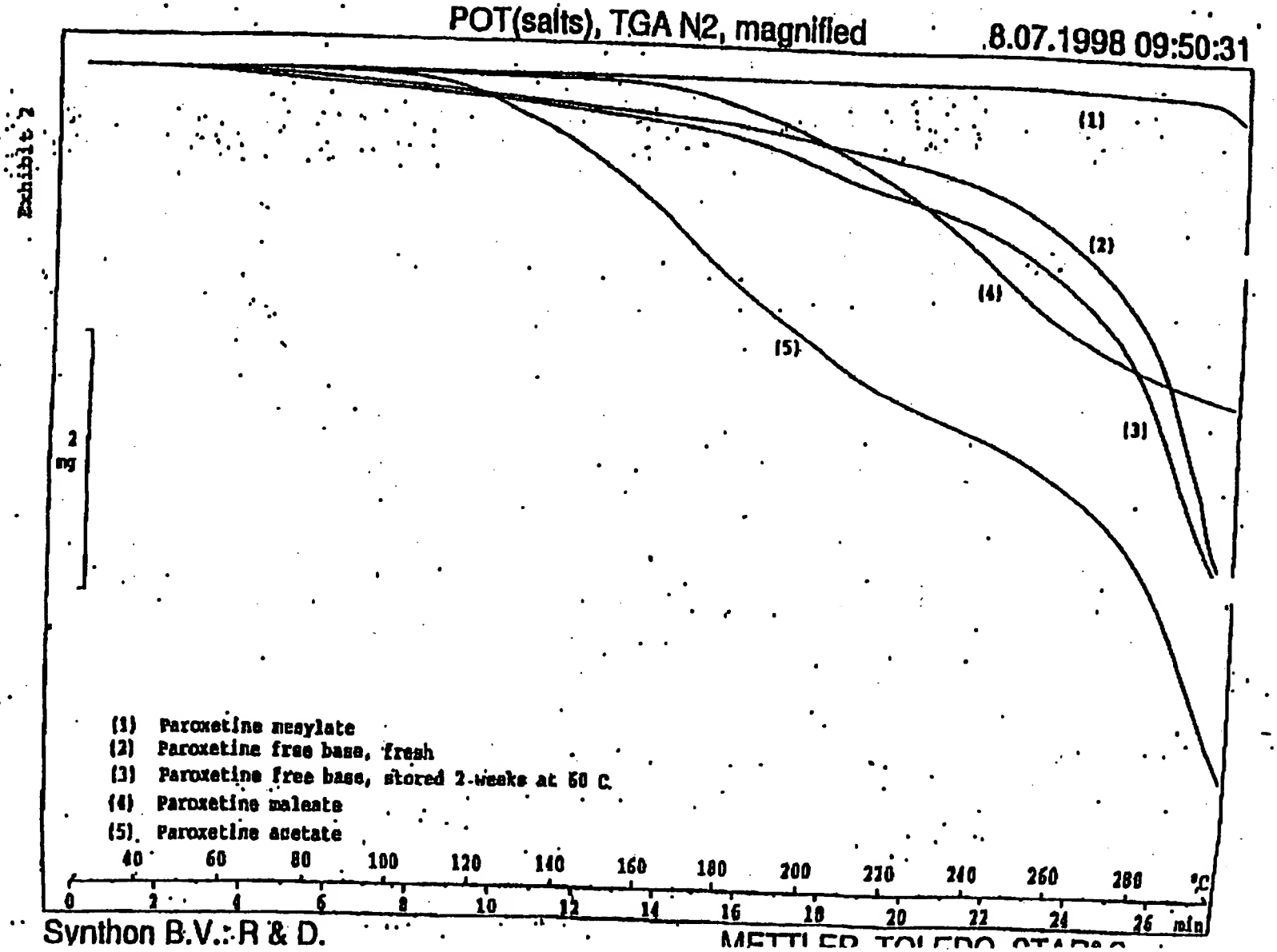
Accordingly, the sulfonate salts demonstrated high and improved stability and are thus suitable for use in pharmaceutical compositions.

5. I further declare that the above statements are true and that all statements made upon information and belief are believed to be true and furthermore that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and may jeopardize the validity of the application or any patent issuing thereon.

22/9/1998
Date

Theodorus Hendricus A. Peters


POT(salts),TGA N2, total
03.07.1998 14:06:46
Exhibit 1
(1)
(2)
(3)
(4)
(5)
(6)
(7)
(8)
(9)
(10)
10 mg
(1) Paroxetine mesylate
(2) Paroxetine besylate
(3) Paroxetine tosylate
(4) Paroxetine parachlororo besylate
(5) Paroxetine hydrochloride henihydrate
(6) paroxetine free base
(7) Paroxetine maleate
(8) Paroxetine fumarate
(9) paroxetine tartrate
(10) Paroxetine acetate
20 40 60 80 100 120 140 160 180 200 220 240 260 280 °C
0 2 4 6 8 10 12 14 16 18 20 22 24 26 min
Synthon B.V.: R & D.
METTLER TOLEDO STAR° System



Synthon B.V.: R & D.

METTLER TOLEDO STAR^e S